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Original article

# C index is associated with both short-term and long-term renal functional outcome after partial nephrectomy

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A B S T R A C T

*Objectives:* Partial nephrectomy is the standard treatment for the small renal mass. C index, one of the nephrometric systems, was found to be associated with short-term renal functional outcome after laparoscopic partial nephrectomy. We conducted this study to externally validate the application of C index as a prognostic factor of long-term renal functional outcome after open partial nephrectomy (OPN) for small renal mass.

*Materials and Methods:* The medical records of 65 consecutive patients undergoing OPN from June 2004 to November 2011 were reviewed. C index was calculated on preoperative computed tomography or magnetic resonance images. The estimated glomerular filtration rate was calculated using the modification of diet in renal disease 2 equation. Short-term and long-term renal functional outcomes were assessed by the nadir estimated glomerular filtration rate within postoperative 1 week and 1 to 2 years. The correlation between C index, perioperative parameters, and renal functional outcomes were examined.

*Results:* The median C index in our cohort was 2.2. C index was associated with operative time, cold ischemia time, estimated blood loss, and length of hospital stay ($p = 0.03$, 0.001, 0.001, and 0.02, respectively). On logistic linear regression analysis, C index ($p = 0.01$) and operative time ($p < 0.001$) were associated with the short-term percent decrease of the estimated glomerular filtration rate, whereas *C* index ($p = 0.03$) was associated with the long-term percent decrease of the estimated glomerular filtration rate. Under the criteria of C index $\leq 2.5$, the sensitivity/specificity were 83.3%/53.8% and 80%/52% in predicting chronic kidney disease stage 3 or greater in the short-term and long-term follow-up, respectively. Moreover, the mean long-term percent decrease of the estimated glomerular filtration rate in patients with C index $\leq 2.5$ was much higher compared with that of patients with C index $> 2.5$ (18.1% vs. 0%, $p = 0.001$).

*Conclusion:* C index could serve as an indicator for both short-term and long-term renal functional decrease after OPN. For patients with C index $\leq 2.5$, a comprehensive analysis of vascular anatomy and planning for dissection are crucial in preoperative assessment, and every effort should be exerted to minimize renal parenchymal damage during surgery.



## 1. Introduction

The incidence of small renal mass (SRM), generally defined as an enhancing renal mass $\leq 4$ cm, has increased substantially over the past few decades owing to the widespread use of modern imaging procedures.[1] Approximately 80% of SRM is malignant, but there is no specific imaging features to identify the mass as malignant or benign tumor.[1] According to the American Urological Association guidelines in 2009 and the European Association of Urology guidelines in 2010, complete surgical excision by open partial nephrectomy (OPN) is the standard treatment for SRM, whereas laparoscopic partial nephrectomy (LPN) is offered as an alternative in experienced centers and robot-assisted partial nephrectomy

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**Table 1**
Patient demographics and functional outcomes.

| | |
|---|---|
| Number of patients | 51 |
| Gender (female/male) | 20:31 |
| Mean age (range) (y) | 57.9 (25–83) |
| Median tumor diameter (range) (cm) | 3.1 (1.5–4) |
| Median C index (range) | 2.2 (1–8) |
| Mean operative time (range) (min) | 258 (155–540) |
| Mean cold ischemia time (range) (min) | 39.5 (17–71) |
| Mean estimated blood loss (range) (mL) | 239 (50–1600) |
| Complication (*n*) | 9 |
| Mean length of hospital stay (d) | 10.6 (7–44) |
| Mean preoperative eGFR (mL/min/1.73 $m^2$) | 82.7 (17–137) |
| Mean postoperative eGFR (mL/min/1.73 $m^2$) | |
| Within 1 wk | 71.4 (14–132) |
| Within 1–2 y | 76.9 (24–115) |

(PN) is still undergoing evaluation.[2,3] Simmons et al[4] proposed a nephrometric system, C index, to evaluate the surgical complexity during LPN. C index is also associated with renal functional outcome within 1 week after LPN.[5] We performed this study to externally validate the application of C index as a prognostic factor of long-term renal functional outcome after OPN for SRM.

## 2. Materials and methods

We retrospectively reviewed the medical records of 65 consecutive patients with SRM who underwent OPN by six surgeons from June 2004 to November 2011 in China Medical University Hospital. Inclusion criteria were unilateral, localized, sporadic, and solid renal mass with enhancement on computed tomography or magnetic resonance images. OPN was performed due to suspicion of malignancy. As for surgical techniques, patients received perioperative hydration, and mannitol was administered just before renal artery clamping. The renal artery was occluded by an atraumatic bulldog clamp, and then renal surface cooling was achieved with sterile ice slush. After the cold ischemic environment was set, the renal mass was resected with a 5-mm margin of normal tissue. Patients' age, gender, comorbidity of diabetes or hypertension, and perioperative parameters—including operative time, cold ischemia time, estimated blood loss, complications, and length of hospital stay—were recorded. After the operation, the patients were followed up at our clinic for imaging studies and renal function. The estimated glomerular filtration rate (eGFR) was assessed by the modification of diet in renal disease 2 (MDRD 2) equation [eGFR (mL/min/1.73 $m^2$) $= 175 \times \text{Cre}^{(-1.154)} \times \text{age}^{(-0.203)}$ ($\times 0.742$ if female)], and the stage of chronic kidney disease (CKD) was defined according to the definition provided by the National Kidney Foundation.[6,7] Short-term and long-term renal functional outcomes were defined as the nadir eGFR within 7 days of operation and between postoperative 1 and 2 years, respectively. C index, defined as the ratio of the distance between the tumor and kidney center to tumor radius, was calculated according to computed tomography or magnetic resonance images. We conducted Spearman correlations to assess the relationship between C index and perioperative parameters. Logistic linear regression analysis was done to evaluate the relevant parameters for short-term and long-term renal function. A receiver operating characteristic curve was used to determine the cutoff value of C index in predicting CKD stage 3 or greater. Statistical analysis was performed using Statistical Product and Service Solution (SPSS), version 17.0, and a $p$ value $< 0.05$ was considered statistically significant. The protocols of this study were approved by the Ethics Committee of China Medical University Hospital.

**Table 2**
Distribution of preoperative and postoperative CKD stages.

| | Overall no. (%) | | |
|---|---|---|---|
| | Preoperative | Postoperative 1 wk | Postoperative 1–2 y |
| Stage 1 (eGFR ≥ 90) | 21 (41.2) | 6 (11.8) | 8 (26.7) |
| Stage 2 (eGFR 60–89) | 22 (43.1) | 34 (66.7) | 17 (56.7) |
| Stage 3 (eGFR 30–59) | 7 (13.7) | 9 (17.6) | 4 (13.3) |
| Stage 4 (eGFR 15–29) | 1 (2.0) | 1 (2.0) | 1 (3.3) |
| Stage 5 (eGFR < 15) | 0 | 1 (2.0) | 0 |

**Table 3**
Correlation between C index and perioperative parameters.

| | Spearman's rho | *p* |
|---|---|---|
| Operative time | −0.407 | 0.03 |
| Cold ischemia time | −0.448 | 0.001 |
| Estimated blood loss | −0.457 | 0.001 |
| Complication | −0.145 | 0.31 |
| Length of hospital stay | −0.338 | 0.02 |

## 3. Results

Of the 65 patients evaluated, 13 were lacking in preoperative digital images or complete recording of perioperative data. One patient with bilateral SRM was also excluded. Table 1 lists the patient demographics and functional outcomes. The median C index was 2.2 (range, 1–8). Four patients in our cohort had major intraoperative bleeding and required blood transfusion. Five patients had postoperative complications, including delayed bleeding, urinary tract infection, urinary leakage, perirenal abscess formation, and pulmonary edema due to fluid overload, respectively. The mean preoperative eGFR was 82.7 mL/min/1.73 $m^2$ (range, 17–137), and the mean percent change in eGFR was 13.7% within postoperative 1 week and 7% within postoperative 1–2 years. Distribution rates of perioperative CKD stages are shown in Table 2.

Table 3 shows the correlations between C index and perioperative parameters. We found that C index was correlated with operative time ($p = 0.03$), cold ischemia time ($p = 0.001$), estimated blood loss ($p = 0.001$), and length of hospital stay ($p = 0.02$), whereas C index had no impact on the complication rate ($p = 0.31$).

As for renal functional outcome after OPN, we found that gender, age, C index, operative time, and preoperative eGFR were correlated with short-term nadir eGFR, whereas only C index and operative time were correlated with percent decrease of eGFR ($p = 0.01$ and $p < 0.001$, respectively; Table 4). Long-term renal function profiles were available in 30 patients. We found that C index and preoperative eGFR were correlated with long-term nadir eGFR, whereas only C index was correlated with long-term percent

**Table 4**
Analysis for short-term functional outcome.

| | Nadir eGFR | | | Percentage decrease of eGFR | | |
|---|---|---|---|---|---|---|
| | Beta | *T* | *p* | Beta | *t* | *p* |
| Gender | 0.204 | 2.86 | 0.01 | −0.107 | −0.926 | 0.36 |
| Age | −0.173 | −2.457 | 0.02 | 0.085 | 0.768 | 0.45 |
| Diabetes | 0.005 | 0.08 | 0.94 | 0.071 | 0.64 | 0.53 |
| Hypertension | 0.13 | 1.774 | 0.08 | −0.177 | −1.623 | 0.11 |
| Tumor size | −0.025 | −0.285 | 0.78 | 0.121 | 0.85 | 0.4 |
| C index | 0.167 | 2.453 | 0.02 | −0.299 | −2.583 | 0.01 |
| Operative time | −0.259 | −3.57 | 0.001 | 0.494 | 4.263 | <0.001 |
| Cold ischemia time | −0.52 | −0.722 | 0.48 | 0.035 | 0.28 | 0.78 |
| Estimated blood loss | 0.061 | 0.858 | 0.4 | −0.134 | −1.147 | 0.26 |
| Preoperative GFR | 0.568 | 7.958 | <0.001 | 0.216 | 1.981 | 0.05 |

Beta = standardized coefficient.

**Table 5**
Analysis for long-term functional outcome.

| | Nadir eGFR | | | Percentage decrease of eGFR | | |
|---|---|---|---|---|---|---|
| | Beta | *t* | *p* | Beta | *t* | *p* |
| Gender | −0.014 | −0.15 | 0.88 | −0.022 | −0.124 | 0.9 |
| Age | −0.149 | −1.683 | 0.1 | 0.309 | 1.822 | 0.08 |
| Diabetes | −0.032 | −0.361 | 0.72 | 0.085 | 0.47 | 0.64 |
| Hypertension | −0.036 | −0.38 | 0.71 | 0.118 | 0.618 | 0.54 |
| Tumor size | −0.019 | −0.159 | 0.88 | 0.067 | 0.278 | 0.78 |
| C index | 0.253 | 2.945 | 0.01 | 0.391 | −2.245 | 0.03 |
| Operative time | −0.091 | −0.995 | 0.35 | 0.235 | 1.259 | 0.22 |
| Cold ischemia time | 0.003 | 0.023 | 0.98 | 0.003 | 0.012 | 0.99 |
| Estimated blood loss | −0.061 | −0.658 | 0.52 | 0.164 | 0.902 | 0.38 |
| Preoperative GFR | 0.884 | 10.279 | <0.001 | −0.158 | −0.899 | 0.38 |

Beta = standardized coefficient.

**Table 6**
Long-term percent GFR decrease stratified by C index 2.5 cutoffs.

| | No. C index ≤ 2.5 (%) | No. C index > 2.5 (%) | RR |
|---|---|---|---|
| Overall | 16 | 14 | |
| Percentage GFR decrease | | | |
| >30% | 2 (12.5) | 0 | |
| >20% | 3 (18.8) | 0 | |
| >10% | 12 (75) | 2 (14.3) | 5.2 |

GFR = glomerular filtration rate; RR = relative risk.

decrease of eGFR ($p = 0.03$; Table 5). Moreover, patient factors including gender, age, diabetes, hypertension, preoperative GFR, and tumor size as well as surgical factors including operative time, cold ischemia time, and estimated blood loss were not correlated with long-term percent decrease of eGFR (Table 5). In the receiver operating characteristic curve for assessing the predictiveness of C index toward CKD stage 3 or greater, we found that, under the criteria of C index ≤ 2.5, the sensitivity/specificity were 83.3%/53.8% and 80%/52% in the short-term and long-term functional outcomes, respectively (Fig. 1). In addition, the long-term mean percent decrease of eGFR in the group of C index ≤ 2.5 was much higher than that in the group of C index > 2.5 (18.1% vs. 0%, $p = 0.001$), and C index ≤ 2.5 carried a 5.2-fold risk of decrease of eGFR of more than 10% (Table 6).

## 4. Discussion

In order to standardize the description of the anatomical features of a renal tumor, three nephrometric systems have been proposed: R.E.N.A.L., PADUA, and C index systems.[4,8,9] The R.E.N.A.L. system is an itemized readout of tumor features including tumor radius, exophytic extent, nearness to the renal sinus, anterior/posterior location, and location relative to the polar lines. The PADUA system, compared with the R.E.N.A.L. system, further scores the relationship to the sinus fat and collecting system as independent factors. However, the PADUA output is a sum score and thus relatively weak in conveying anatomic information. C index is a comprehensive score calculated by tumor depth and size. Because C index is based solely on measured distances, it is less prone to be affected by the observer's subjectivity.[10] Initially developed as a surrogate of technical complexity during LPN, C index is also associated with short-term functional outcome after LPN.[5] To our knowledge, there is no report in the literature discussing the long-term influence of C index on renal function after PN. Thus, we conducted this study to provide external validation for C index.

Canter et al[11] found that in patients presenting with solid renal tumors, although 88% had normal serum creatinine, 22% of them had CKD stage 3 or greater. In Taiwan, the prevalence of CKD is among the highest in the world, but the awareness rate is low.[12] In our cohort, 15.7% of patients with SRM undergoing PN had CKD stage 3 or greater. Because CKD stage 3 or greater carries a higher risk of cardiovascular events, days of hospitalization, and death, the issue of renal function preservation during PN cannot be overemphasized.[13,14] Our data revealed a decline of renal function due to an ischemic insult in postoperative 1 week and partial recovery in postoperative 1 to 2 years (Table 3). Lane et al[15] also reported that renal function declined immediately after PN and returned to a new steady state generally within 3 weeks. At a mean follow-up of 1.5 years, preoperative GFR, age, gender, absent or poorly functioning contralateral kidney, and warm ischemia time were significant predictors of ultimate renal function.[15] Jeldres et al[16] reported that preoperative renal function, perioperative blood loss, and ischemia time were independent predictors of >25% reduction in GFR after PN. Thompson et al[17] found that longer warm ischemia time was associated with acute renal failure (odds ratio = 1.05 for each 1-minute increase) and new-onset CKD stage 4 for patients with solitary kidney undergoing PN. However, if renal parenchymal preservation is incorporated into the analysis, only preoperative GFR and percent functional volume preservation were reported to be correlated with long-term renal function after PN.[18] In a large

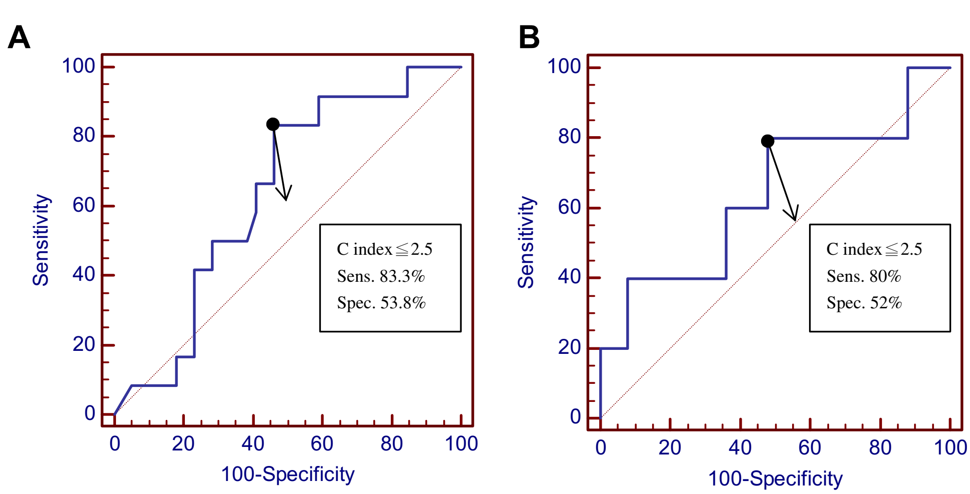


**Fig. 1.** ROC for the predictiveness of C index toward CKD stage 3 or greater. (A) For short-term functional outcome, AUC was 0.638. (B) For long-term functional outcome, AUC was 0.64. AUC = area under the curve; CKD = chronic kidney disease; ROC = receiver operating characteristic curve.

multicenter study, Lane et al[19] found that the percentage of parenchyma preserved ($p < 0.00001$) and preoperative GFR ($p < 0.00001$) were the strongest predictors of renal function after OPN, whereas age ($p = 0.0008$) and tumor size ($p = 0.0003$) play less significant roles.

In the present study, C index ($p = 0.01$) and operative time ($p < 0.001$) were correlated with short-term percent decrease of eGFR, whereas C index ($p = 0.03$) was correlated with long-term percent decrease of eGFR. A lower C index implies that the larger the tumor size and/or the shorter the distance between the tumor and the kidney center, the greater the renal parenchymal reduction would be expected during tumor excision. In fact, the width of the resection margin is irrelevant to disease progression.[20,21] However, a large resection margin has the potential risk of violating the collecting system, causing injury to the hilar vessels, or even hindering the ability of the surgeons to perform PN. Thus, the surgical margin should be kept as minimal as possible to preserve normal renal parenchyma, and intraoperative frozen section analysis may be used as necessary.[22]

The percentage of GFR decrease after PN was reported to range from 5% to 8.8% upon follow-up of 1 to 1.5 years.[15,23,24] In our series, a 7% GFR decrease was noted within postoperative 1 to 2 years. C index <2.5 has been reported to correlate with a 2.2-fold increased risk of a >30% GFR decrease within 1 week after LPN.[5] In our series, we also found that the long-term percent decrease of GFR was much higher in C index $\leq 2.5$ compared with C index $> 2.5$ (18.1% vs. 0%, $p = 0.001$), and C index $\leq 2.5$ carried a 5.2-fold risk of decrease in eGFR of more than 10%. However, our case numbers were too small to show the relative risk of decrease of eGFR of more than 20% or 30%. Nevertheless, C index $\leq 2.5$ showed fair sensitivity (80%) and specificity (52%) in predicting long-term CKD stage 3 or greater. Therefore, patients with C index $\leq 2.5$ should be regarded as having a high risk of significant renal functional reduction. For these high-risk patients, OPN, instead of LPN, may be more suitable in consideration of shortening the ischemia time and minimizing the complication rate.[2,3] Moreover, a comprehensive analysis of vascular anatomy and planning for dissection are very important in order to preserve the normal parenchyma as much as possible. Finally, early lifestyle modification, adjustment of medication, or referral to a nephrologist may be warranted.

It is rather complex to predict the long-term renal function after PN, as it may be confounded by patients' medical comorbidities. However, hypertension, diabetes, body mass index, smoking, and Charlson index were reported not to be correlated with long-term renal functional outcome after PN.[15,25,26] In our series, hypertension and diabetes were not associated with long-term renal functional outcome either. By contrast, although preoperative GFR was correlated with ultimate GFR, it does not play a significant role in determining the percent reduction of GFR.[18,19,26] In fact, the extent of renal parenchymal preservation remains the most important and modifiable factor in determining long-term renal function after PN.[19,26] C index, calculated by the tumor size and depth, may help us to access how much renal parenchyma could be preserved during preoperative planning; however, further research is needed to validate this concept.

The mean cold ischemia time in our study was 39.5 minutes. In line with previous series, cold ischemia time was not associated with long-term renal function impairment.[27,28] Although cold ischemia time up to 2 hours could be tolerated by the kidney, Thompson et al recommended that it should be limited within 35 minutes if technically feasible to decrease the risk of acute renal failure and urinary leakage.[29,30]

There are several limitations in our study. This is a retrospective and single-institution study with small case numbers. We included only patients with renal tumors $\leq$ 4 cm who were undergoing OPN. Future larger-scale studies conducting comparisons between LPN and OPN may be needed to validate these results. Moreover, the most accurate way to determine renal function is by using renal scintigraphy with technetium-99 *m*-mercaptoacetyltriglycine.[31] In consideration of cost-effectiveness, we used the MDRD 2 equation, which was also recommended for the assessment of renal function after nephrectomy.[32]

## 5. Conclusion

C index could serve as an indicator for both short-term and long-term renal functional decrease after OPN. For patients with C index $\leq 2.5$, a comprehensive analysis of vascular anatomy and planning for dissection are crucial in preoperative assessment, and every effort should be exerted to minimize renal parenchymal damage during surgery.

## Conflicts of interest statement

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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